REMARKS

Amendments

Claims 1-62 have been canceled, and claims 63, 72, 74-76 have been amended. Upon entry of the amendment, claims 63-76 will be pending. Support for the amendment to the claims can be found throughout the specification as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Rejections

Rejections under 35 U.S.C. §§ 101

The Examiner has rejected claims 63-70 and 72-76 and because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility.

1. Utility

Applicant respectfully traverses the rejection. Amended claim 1 is drawn to a transgenic mouse whose genome comprises a null endogenous lymphoid specific GPCR allele. According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> . . .

If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)).

The standard for "credible" is defined as:

. . . whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

(MPEP 2107.02, III(B)(emphasis added).

According to the Patent Office's own guidance to Examiners:

Langer and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. [citations omitted] . . . Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false.

Compliance with 35 U.S.C. 101 is a question of fact [citations omitted]. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. . . . To do this, Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered "false" by a person of ordinary skill in the art.

(MPEP 2107.02, III(A)(emphasis added).

Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, of the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under 35 U.S.C. 101.

(MPEP 2107.02, III(B)(emphasis in original and added). The Guidelines additionally provide that:

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (citations omitted), and whether the asserted utility appears to contravene established scientific principles and beliefs. (citations omitted). Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." (citations omitted). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)(reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response).

(MPEP 2107.02, VII)(emphasis added).

Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. An assertion of utility is presumed to be true. The burden is on the Examiner to show that one of ordinary skill would find the asserted utility to be false. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined.

According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
>
> . . .
>
> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of

> tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834)(emphasis added)(copy attached). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Knockout mice are so well accepted as tools for determining gene function that the director of the NIH Chemical Genomics Center of the National Human Genome Research Institute (among others, including Capecchi, Bradley, Joyner, Nagy and Skarnes) has proposed creating knockout mice for all mouse genes:

> Now that the human and mouse genome sequences are known, attention has turned to elucidating gene function and identifying gene products that might have therapeutic value. The laboratory mouse (Mus musculus) has had a prominent role in the study of human disease mechanisms throughout the rich, 100-year history of classical mouse genetics, exemplified by the lessons learned from naturally occurring mutants such as agouti, reeler and obese. The large-scale production and analysis of induced genetic mutations in worms, flies, zebrafish and mice have greatly accelerated the understanding of gene function in these organisms. Among the model organisms, the mouse offers particular advantages for the study of human biology and disease: (i) the mouse is a mammal, and its development, body plan, physiology, behavior and diseases have much in common with those of humans; (ii) almost all (99%) mouse genes have homologs in humans; and (iii) the mouse genome supports targeted mutagenesis in specific genes by homologous recombination in embryonic stem (ES) cells, allowing genes to be altered efficiently and precisely.
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> . . .
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> A coordinated project to systematically knock out all mouse genes is likely to be of enormous benefit to the research community, given the demonstrated power of knockout mice to elucidate gene function, the frequency of unpredicted phenotypes in knockout mice, the potential economies of scale in an organized and carefully planned project, and the high cost and lack of availability of knockout mice being made in current efforts.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 921)(emphasis added)(copy attached).

With respect to claims drawn to transgenic mice having a null allele, the following comments from Austin are relevant:

> **Null-reporter alleles should be created**

> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.
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> (p. 922)(emphasis in original, emphasis added).

Research tools such as knockout mice are clearly patentable, as noted by the Patent Office:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function), one that is clearly recognized by those skilled in the art.

For example, according to the Molecular Biology of the Cell (Albert, 4th ed., Garland Science (2002)) (copy of relevant pages attached), one of the leading textbooks in the field of molecular biology:

> Extensive collaborative efforts are underway to generate comprehensive libraries of mutation in several model organisms including . . . the mouse. The ultimate goal in each case is to produce a collection of mutant strains in which every gene in the organism has either been systematically deleted, or altered such that it can be conditionally disrupted. Collections of this type will provide an invaluable tool for investigating gene function on a genomic scale.
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> (p. 543)(emphasis added).

According to Genes VII (Lewin, Oxford University Press (2000)) (copy of relevant pages attached), another well respected textbook in the field of genetics:

> The converse of the introduction of new genes is the ability to disrupt specific endogenous genes. Additional DNA can be introduced within a gene to prevent its expression and to generate a null allele. Breeding from an animal with a null allele can generate a homozygous "knockout", which has no active copy of the gene. This is a powerful method to investigate directly the importance and function of the gene.

(p. 508)(emphasis added).

According to Joyner (Gene Targeting: *A Practical Approach*, Oxford University Press 2000) (copy of relevant pages attached),:

> Gene targeting in ES cells offers a powerful approach to study gene function in a mammalian organism.

(preface)(emphasis added).

According to Matise et al. (*Production of Targeted Embryonic Stem Cell Clones* in Joyner, Gene Targeting: *A Practical Approach*, Oxford University Press 2000)(copy of relevant pages attached):

> The discovery that cloned DNA introduced into tissue culture cells can undergo homologous recombination at specific chromosomal loci has revolutionized our ability to study gene function in cell culture and *in vivo*. . . . Thus, applying gene targeting technology to ES cells in culture affords researchers the opportunity to modify endogenous genes and study their function *in vivo*.

(p. 101)(emphasis added).

According to Crawley (What's Wrong With My Mouse *Behavioral Phenotyping of Transgenic and Knockout Mice*, Wiley-Liss 2000) (copy of relevant pages attached):

> Targeted gene mutation in mice represents a new technology that is revolutionizing biomedical research.
>
> Transgenic and knockout mutations provide an important means for understanding gene function, as well as for developing therapies for genetic diseases.

(p. 1, rear cover)(emphasis added).

2. Well-Established Utility

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

Applicant submits that in light of arguments of record that a person of ordinary skill in the art would immediately appreciate why the invention is useful. Applicant submits that it cannot be reasonably debated that a person of ordinary skill in the art would not immediately appreciate why the invention is useful: for determining gene function.

3. Specific

The Examiner argues that the asserted utility "applies to any knockout mouse is not specific to the claimed invention, the GPCR knockout mouse" (page 5).

Applicant does not agree. "All knockout mice" cannot be used to study the function of the GPCR gene. The use of each knockout mouse is specific to the particular gene which is disrupted.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the GPCR -/- mouse to study the function of the GPCR gene and the association of the GPCR gene with, for example, lymphocyte cellular infiltration, is specific to this mouse. Even if there were many other genes associated with this condition, only a GPCR knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene in these conditions. The Examiner is respectfully requested to explain (1) how the asserted utility of characterizing the function of the GPCR gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the GPCR gene with lymphocyte cellular infiltration would be applicable to all other knockout mice. The Examiner is requested to explain how all other knockout mice would be used to study the function of the GPCR gene.

In addition, the mice within the scope of claim 74 contain a *lacZ* gene. Their use in studying gene expression is clearly recognized by those skilled in the art:

> **Null-reporter alleles should be created**
> The project should generate alleles that are as uniform as possible, to allow efficient production and comparison of mouse phenotypes. The alleles should achieve a balance of utility, flexibility, throughput and cost. A null allele is an indispensable starting point for studying the function of every gene. Inserting a reporter gene (e.g., P-galactosidase or green fluorescent protein) allows a rapid assessment of which cell types normally support the expression of that gene.

(Austin et al., Nature Genetics (2004) 36(9):921-24, 922)(emphasis in original; emphasis added)(copy attached). As cited in Austin, and as is well known by one of ordinary skill, the purpose of expression analysis is to determine where the gene is expressed.

As is well understood in the art, the *lacZ* gene is inserted into the endogenous gene. In this case, the *lacZ* gene was inserted into the locus of the GPCR gene. Expression is driven by the endogenous promoter. Expression of the *lacZ* gene indicates where the GPCR gene is expressed. This use is specific for this mouse – knockout mice in general cannot be used for this purpose. The Examiner is respectfully requested to explain how all other knockout mice would be used to study expression of the GPCR gene.

4. Substantial

The Examiner argues that the asserted utilities are not substantial (page 5).

Applicant does not agree. According to the MPEP, under the section entitled "Substantial Utility":

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. . . . the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":
>
> (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved;
>
> Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations in other cases to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility

> requirement. See, e.g., Brenner v. Manson, 383 U.S. 519, 534-35, 148 USPQ 689, 695 (1966). Rather, **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit **should be accepted as sufficient,** at least with regard **to defining a "substantial" utility.**
>
> (MPEP § 2107.01 I)(emphasis added).

The MPEP additionally provides:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., the are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.
>
> (MPEP 2107.01, I)

A use is not substantial where further research is required to identify any use. This is not the case in the present application. Knockout mice have a well-known use in the study of gene function. In the present case, the instant invention does not require further research to establish a utility. Applicant has determined that the GPCR gene is associated with, for example, lymphocyte cellular infiltration of numerous organs. No further research is required to establish any use. Whether additional research is required to identify therapeutic agents targeting the GPCR gene or to further characterize the function of the GPCR gene is irrelevant to whether the claimed invention has satisfied the utility requirement.

Commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee

Deltagen has been clearly established. The claimed mouse has been extensively analyzed using the tests set forth in the Examples. This data has been incorporated into Deltagen's commercial database product, DeltaBase. This database has been subscribed to by at least three of the world's largest pharmaceutical companies, Merck, Pfizer and GSK. In addition, at least one (1) pharmaceutical company has ordered the presently claimed mouse. This acceptance more than satisfies the practical utility requirement of section 101 as **it cannot be reasonably argued that a claimed invention which is actually being used by those skilled in the art has no "real world" use**. (see, for example, Phillips Petroleum Co. v. U.S. Steel Corp., 673 F. Supp. 1278, 6 U.S.P.Q.2d 1065, 1104 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1980)("lack of practical utility cannot co-exist with infringement and commercial success); (Lipscomb's Walker on Patents, §5:17, p. 562 (1984)("Utility may be evidenced by sales and commercial demand.")

Applicant notes that the Examiner has not objected to the Applicant's statement that the claimed transgenic mice have been delivered to pharmaceutical customers. Applicant respectfully submits that the fact of such commercial sales is admitted. However, Applicant is also submitting herewith, as evidence of such sales and purpose of such use, a Rule 132 Declaration from Robert Driscoll, Vice President of Intellectual Property & Legal Affairs of Assignee, Deltagen.

The Examiner argues that *Phillips Petroleum* and *Brenner* do not support the notion that a commercial sale validates the patentable utility of a claimed invention.

The Examiner's statement is conclusory as the Examiner has not explained why these cases do not support patentable utility based on commercial sale and use.

The Examiner asserts the claimed mice are not useful as research tools because using a product for further research is not a "substantial utility;" and that further study would be required to determine the function of the gene (page 7).

Applicant does not agree. First, it is wholly untrue that further research is required in order to confirm the utility of the claimed mouse in determining the function of GPCR gene. The value of knockout mice in determining gene function is well established and accepted in the art. This is demonstrated by the references cited above. The Examiner has failed to provide sufficient factual support for the position that it is more likely than not that a person of skill in

the art would doubt that Applicant's asserted utility is specific and substantial, which is the standard for establishing a *prima facie* case. See MPEP § 2107.02, IV.

Second, Applicant is claiming a transgenic mouse, and not the GPCR receptor or nucleic acid sequence. The Examiner must differentiate between the utility of the transgenic mouse and the utility of the target gene. "The claimed invention is the focus of the assessment of whether an applicant has satisfied the utility requirement." (MPEP 2107.02, I) That the claimed transgenic mouse can be used in a research setting to further characterize the GPCR gene does not mean that the mouse lacks patentable utility. Further characterization (involving "basic research") of the mouse itself is not necessary in order to confirm its utility in studying the function of the GPCR receptor gene.

According to the MPEP:

> **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit **should be accepted as sufficient,** at least with regard to defining a "substantial" utility.

Certainly providing an *in vivo* model for studying the function of the GPCR receptor gene is a reasonable use.

In addition, the MPEP specifically cautions Examiners not to get confused by labeling inventions as research tools:

> Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

Applicant respectfully submits that the Examiner has done what the MPEP specifically cautions against, by providing: "[a]n assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense."

The Examiner argues that scientific "utility" is not the same as "patentable utility" or a "well-established" utility (page 6).

Applicant does not agree. According the Utility Guidelines,

> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

As acknowledged by the Examiner, the use of knockout mice to study gene function is well-known – i.e., the mouse has scientific utility. If the asserted use is considered credible and accepted by the scientific community, how can such a use not be regarded as substantial? Applicant submits that if a claimed invention has scientific utility, it necessarily follows that the invention has patentable utility.

5. In re Brana

The Examiner also argues that the fact pattern in *Brana* does not apply to the fact pattern of the instant application because in *Brana* the specification did disclose a specific and substantial use for the claimed compound (pp. 6-7).

Applicant submits that the legal principles as well as the facts of *Brana* are applicable to the present case. In *Brana*, the Board held that the applicant's specification failed to disclose a specific disease against which the claimed compounds were useful. The Federal Circuit reversed and held that the mouse tumor model represented a specific disease against which the compounds were effective. In the present case, the Examiner has argued that Applicant failed to demonstrate a link between the GPCR gene and any of the recited phenotypes. It is Applicant's position that a mouse demonstrating, for example, lymphocyte cellular infiltration of liver tissue and/or pancreatic tissue, is sufficient to establish the animal's use as a model for immunological disorders. As in *Brana*, confirmation of the phenotype in humans is unnecessary.

As in *Brana*, the PTO did not regard the asserted use to be credible:

> Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, see supra note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested in vivo for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this

particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in Kirk and Kawai. See, e.g., Cross v. Iizuka, 753 F.2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in Kirk and Kawai.)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

(*Brana* at 1440). Thus, the PTO was aware of the asserted use against the mouse tumor lines but did not find the use specific – as in the present case.

The court went on:

The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordinary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious decision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

(*Brana* at 1443-44). The court's position is reflected in the MPEP: if an "assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (MPEP § 2107, II (A)(3); II (B)(1)). If it is well known to those skilled in the art that knockout mice are useful for studying gene function, then those skilled in the art would certainly regard such use as credible, specific and substantial. Nothing more is required to satisfy the statutory requirement. Applicant submits that, as in *Brana*, one skilled in the art would find the asserted use credible, substantial and specific.

6. Summary

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying the function of the target protease gene with respect to the cited phenotypes as well as studying gene expression; and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the amendments and arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected the claims because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility for the reasons set forth in the utility rejection. Applicants respectfully traverse the rejection. For the reasons set forth above, it is Applicant's position that the claimed invention satisfies the utility requirement. Therefore, one skilled in the art would know how to use the invention.

With regard to predictability of phenotype, the Examiner argues that "although making a mouse with a null allele by a replacement vector usually knockout[s] the gene, the phenotype is

still unpredictable because it not only depends on the function of the endogenous gene but also what exogenous DNA the gene is replaced with."

Applicant does not agree. Enablement is evaluated with regard to the claimed invention: in this case, a transgenic mouse having a null GPCR allele. By definition, the claimed mouse is one having the GPCR gene disrupted by the method of gene targeting (specification, page 9, lines 30-33). By definition, a null allele is one where the function has been ablated. Applicant submits that the phenotype of a transgenic mouse having a null GPCR allele is reproducible. Applicant submits that the Examiner needs to differentiate between predicting *a priori* the phenotype of a transgenic and reproducibility of the phenotype of the claimed mouse. Moreover, the Examiner has provided no evidence whatsoever to support the position that a null allele is affected by the type of exogenous DNA introduced via gene targeting.

With regard to the effect of background on phenotype, Applicant points out that amended claim 1 does not recite phenotypes. The specification clearly enables the making and use of a transgenic mouse having a null GPCR allele.

The dependent claims recite certain observed phenotypes such as lymphocyte cellular infiltration of the liver and/or pancreatic tissues. The Examiner has not cited any evidence that background affects these non-behavioral phenotypes.

Applicant additionally points out that all of the employees and consultants involved in Deltagen's pathology group are either MD's or DVM's, and many in addition hold PhD degrees. At least sixteen (16) of the employees or consultants are board certified ACVP or ABP. Unless the Examiner has reason to doubt the credibility of the reported results, the burden remains on the Examiner to set forth a *prima facie* case. Unless and until the Examiner is able to do so, the Applicant respectfully requests withdrawal of the rejections.

The Examiner argues that "Applicant clearly misconstrues the examiner's position of the phenotype being the essential element of the claimed invention." The Examiner argues that "the claim must recite the phenotype of the claimed mouse because one skilled in the art would not know how to use a knockout mouse without any phenotypes." (page 8).

Applicant does not agree. The Examiner is confusing the role of the claims and the specification. The claims define the invention. The specification teaches one how to make and use the claimed invention. There is no requirement – and the Examiner has not cited any – for

the proposition that a claim to a composition of matter need recite properties inherent to that composition.

Applicant submits that the specification fully enables the claimed invention and respectfully requests withdrawal of the rejections.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 15 and 21 stand rejected for allegedly failing to comply with the written description requirement.

The claims have been amended. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 70 has been rejected as allegedly being indefinite. Claim 63 no longer recites "visible marker" rendering the rejection moot.

Objections

Claim 76 has been amended to recited dependency on claim 63.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 502775.

Respectfully submitted,

6-10-05

Date

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